



ORIGINAL ARTICLE

Irritable bowel syndrome and risk of glaucoma: An analysis of two independent population-based cohort studies

Zachary E. McPherson^{1,2,3}  | Henrik T. Sørensen⁴ | Erzsébet Horváth-Puhó⁴ | Ashish Agar⁵ | Minas T. Coroneo^{5,7} | Andrew White^{6,8} | Ian C. Francis^{5,7} | Louis R. Pasquale⁹ | Jae H. Kang¹⁰ | Sven Pettersson² | Nicholas J. Talley¹ | Mark A. McEvoy^{1,3} 

¹School of Medicine and Public Health, The Centre for Clinical Epidemiology and Biostatistics, The Australian GastroIntestinal Research Alliance (AGIRA), The University of Newcastle, Callaghan, New South Wales, Australia

²Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore

³Rural Health School, La Trobe University, Bendigo Victoria, Australia

⁴Department of Clinical Epidemiology, Aarhus University, Aarhus, Denmark

⁵Department of Ophthalmology, Prince of Wales Hospital, Randwick, New South Wales, Australia

⁶Department of Ophthalmology, Westmead Hospital, Westmead, New South Wales, Australia

⁷The School of Medicine, The University of New South Wales, Kensington, New South Wales, Australia

⁸Westmead Institute for Medical Research, University of Sydney, Sydney, New South Wales, Australia

⁹Department of Ophthalmology, Icahn School of Medicine at Mount Sinai, New York, New York, USA

¹⁰Channing Division of Network Medicine, Department of Medicine, Brigham & Women's Hospital and Harvard Medical School, Boston, Massachusetts, USA

Correspondence

Mark McEvoy, Rural Health School, La Trobe University, PO Box 199, Bendigo, VIC 3552, USA.

Abstract

Objective: Irritable bowel syndrome (IBS) is a chronic disorder associated with an abnormal gastrointestinal microbiome. Microbiome–host interactions are known to influence organ function including in the central nervous system; thus, we sought to identify whether IBS may be a risk factor for the development of glaucoma.

Design: Two prospective cohort studies.

Subjects: The 1958 United Kingdom Birth Cohort (UKBC; 9091 individuals) and the Danish National Registry of Patients (DNRP; 62,541 individuals with IBS and 625,410 matched general population cohort members).

Methods: In the UKBC, participants were surveyed throughout life (including at ages 42 and 50). The DNRP contains records of hospital-based contacts and prescription data from the national prescription database.

Main Outcome Measure: The main outcome measure was incidence of glaucoma. In the UKBC, incident glaucoma at age 50 ($n = 48$) was determined through comparison of survey responses at ages 42 and 50 years. In the DNRP, glaucoma was assessed by hospital diagnosis ($n = 1510$), glaucoma surgery ($n = 582$) and initiation of glaucoma medications ($n = 1674$).

Results: In the UKBC, the odds ratio (OR) of developing glaucoma between ages 42 and 50 in persons with a chronic IBS diagnosis was increased [OR: 5.84, 95% confidence interval (CI): 2.26–15.13]. People with an IBS diagnosis in the DNRP had a hazard ratio (HR) of 1.35 for developing physician-diagnosed glaucoma (95% CI: 1.16–1.56), an HR of 1.35 for undergoing glaucoma surgery (95% CI: 1.06–1.70) and an HR of 1.19 for initiating glaucoma medication (95% CI: 1.03–1.38).

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Email: M.McEvoy@latrobe.edu.au

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Conclusions: In two large European cohort studies, IBS is a risk factor for glaucoma.

KEYWORDS

cohort studies, glaucoma, irritable bowel syndrome, risk factor

INTRODUCTION

Irritable bowel syndrome (IBS) is a chronic disorder characterised by abdominal pain and bowel dysfunction. Evidence is accumulating that the gastrointestinal microbiome of the IBS patients is abnormal compared to healthy populations.^{1,2} Furthermore, immune activation may occur, with circulating small intestinal homing T cells and cytokine release.^{3,4} Importantly, the gut microbiome regulate both the concentration of neuroprotective neurotrophins^{5,6} and the activity of microglia⁷ in the central nervous system (CNS). This suggests that dysbiosis of the gut microbiome could play a role in neurodegenerative disease. It is possible that gut-mediated neuroprotection may extend to the retina and the optic nerve. As well, this neuroprotection may be lost or diminished by changes in the gut microbiome, as observed in IBS.

Glaucoma is a neurodegenerative disease affecting the optic nerve.⁸ Globally, it is a leading cause of irreversible blindness; approximately one in the six persons with glaucoma will become blind during their lifetimes.⁹ Elucidation of novel risk factors is needed to inform clinical decision-making regarding screening for glaucoma and also may provide insights into potential disease pathways, paving the way for the development of neuroprotective interventions.¹⁰ Interactions between host and microbiome are known to influence human health.^{11,12} A recent study of 30 people with primary open-angle glaucoma compared to 30 healthy controls found differences in the microbial contents of their faecal microbiome.¹³ Recent work has demonstrated that the optic nerve degeneration can be driven by microbiome-dependent autoimmune mechanisms.¹⁴

This research aimed to examine whether there is an association between IBS and glaucoma, an association not yet explored in the literature.

METHODS

Overview

This study examined the risk of a glaucoma diagnosis in adults with and without an IBS diagnosis who participated in the United Kingdom-based 1958 Birth Cohort (UKBC) or who had records in the Danish National Registry of Patients (DNRP).

Key summary

What is already known

- Irritable bowel syndrome (IBS) is associated with microbiome changes in microbiome composition and diversity.
- Alteration in microbiome composition may influence organ function including the central nervous system.
- Glaucoma is a potentially blinding illness with treatment options that address only one known risk factor, namely intra-ocular pressure.

What this study adds

- Irritable bowel syndrome may be a risk factor for the development of glaucoma.
- Recognising IBS as a risk factor may allow for earlier detection of glaucoma (often asymptomatic until late in the disease process).
- If glaucoma is confirmed to be associated with IBS, identifying the underlying mechanisms may provide new insights into the etiopathogenesis of both conditions and may lead to new therapeutic approaches for the early treatment of glaucoma.
- Investigation is required to determine whether the IBS patients are at elevated risk for developing other neurodegenerative illnesses.

Data sources

The 1958 UK Birth Cohort

The UKBC was initiated in 1958 with the enrolment of approximately 17,500 children born in the United Kingdom during a single week in 1958. All children delivered were eligible for enrolment and 98.7% of potential cohort members participated.¹⁵ The majority of data collected by the UKBC (and all data analysed by this study) is generated by self-reported participant questionnaire responses at each follow-up wave.

Of the 16,091 possible respondents, 11,419 (71%) completed the survey at age 42. At age 50, 9790 of the 15,806 (62%) responded. Attrition occurred due to mortality or participants moved to a new address and did not respond to efforts to trace them.¹⁵ The UKBC is described in detail by Power and Elliott.¹⁶

The UK data service provides access to UKBC data for non-commercial use.¹⁷⁻²⁰

The Danish cohort

The DNRP is a registry that has recorded all hospital-based care provided to the residents of Denmark, including outpatient clinic and emergency department care since 1995. The registry includes both primary and secondary discharge diagnoses reported by treating hospitals. During the enrolment period for the present study (1 January 1995 to 30 November 2013), a cumulative population of 7,298,249 persons had records in the DNRP. The scope and the methodology of the DNRP are explained in greater detail in the review by Schmidt et al.²¹

This study prospectively included Danish residents with a hospital discharge diagnosis of IBS ($n = 62,541$) in the DNRP, during 1995–2013. Two comparison cohorts also were identified: an age- (birth year) and gender-matched general population comparison cohort members drawn from the general population (10 cohort members per IBS patient, $n = 625,410$) and an age- (birth year) and gender-matched comparison cohort members who had a hospital diagnosis of cholelithiasis recorded in the DNRP during the enrolment year of the IBS patient (one cohort member per IBS patient, $n = 62,541$).

Approval for the use of DNRP data was granted by the Danish Data Protection Board.

Identification of variables

Identification of IBS

In the UKBC, IBS was assessed by self-report in surveys administered at ages 42 and then again at surveys administered at age 50 (see Supplementary Methods for full explanation). Participants who met the criteria for a case of IBS at or before the age of 42 and also at the age of 50 were considered to have 'chronic IBS'.

In the DNRP, all patients with an inpatient or outpatient hospital clinic contact for IBS from 1 January 1995 to 30 November 2013 were enrolled in the study. The IBS was classified based on International Classification of Diseases (ICD)-8 codes up to 1993 and subsequently by ICD-10 codes (Supplementary Methods). The date of the first entry of an IBS diagnosis code into the DNRP was defined as the IBS diagnosis date.

Identification of glaucoma

In the UKBC, glaucoma was assessed by self-report in surveys administered at ages 42 and 50 (Supplementary Methods). A

participant was considered to have a case of 'incident glaucoma' if they met the criteria for glaucoma at age 50 but not at age 42.

In the DNRP, three definitions were used to identify glaucoma: (1) physician diagnoses of primary open-angle glaucoma made in discharge diagnoses or hospital outpatient clinics using ICD-8 and ICD-10 codes, as recorded in the DNRP; (2) surgical procedures performed in hospitals, documented using the Nordic Classification of Surgical Procedures; and (3) first-time redemption of a prescription for a medication used to treat glaucoma, as recorded in the Danish National Health Service Prescription Registry using the Anatomical Therapeutic Chemical classification (see Supplementary Methods). As medication data became available in 2004, analyses that relied on redeemed prescriptions to identify glaucoma were restricted to 2005–2013.

Covariates

A Directed Acyclic Graph (Figure S1) was used to assess covariates for their potential to confound the association. Potential confounders included age, ethnicity, gender, sleep apnoea and diabetes mellitus.

The covariates available in the UKBC analysis were age, gender, diabetes mellitus, ethnicity and smoking. Age was accounted for by the study design. Gender was recorded at the time of enrolment. Diabetes mellitus (coded as yes or no) was identified by self-report and was assessed at ages 7, 11, 16, 42 and 50 years. Ethnicity was ascertained in the survey administered at age 42. Smoking was ascertained in the survey administered at age 50, when participants were asked if they currently smoked and if they had ever smoked.

The covariates available in the DNRP analysis were age, gender, diabetes mellitus, sleep apnoea, chronic obstructive pulmonary disease (COPD) and steroid usage. Age and gender were accounted for by the study design. Data on diabetes mellitus, sleep apnoea and COPD were collected from diagnoses recorded in the DNRP (ICD-8 and ICD-10 codes), and diabetes was also assessed and identified with prescription data recorded in the Danish National Health Service Prescription Registry (Anatomical Therapeutic Chemical classification system codes; see Table S1).

Statistical analyses

As the UKBC and the DNRP differ significantly in their design, statistical approaches were individualised to each dataset.

In the UKBC analysis, the primary exposures of interest were IBS at or before the age of 42 and chronic IBS. The primary outcome measure was a diagnosis of incident glaucoma occurring between the ages of 42 and 50. Logistic regression models were used to assess the odds of a glaucoma diagnosis among persons with a diagnosis of IBS compared to those without IBS. Bivariate exact logistic regression was used to compute the crude unadjusted effect, and multivariable-adjusted exact logistic regression was used to compute the odds of glaucoma after adjusting for potential confounders.

Due to the small number of glaucoma cases, it was not possible to adjust for smoking history or ethnicity in multivariable-adjusted models. To assess these covariates, we performed subgroup analyses using the multivariable-adjusted logistic regression model. The first subgroup analysis was limited to white participants. As smoking is a variable that may lead to an indirect causal pathway (Figure S1), a second subgroup analysis was limited to non-smokers to exclude this indirect pathway.

Participants with missing data were removed in all analyses. Results were reported as prevalence odds ratios (ORs) with 95% confidence intervals (CIs). Statistical analyses were completed using STATA software version 15.1 (StataCorp LLC).

The DNRP analysis examined the time to incident glaucoma in hospital-diagnosed IBS patients and comparison cohorts, with death as a competing risk. The IBS patients were compared to two comparison cohorts: members of the general population matched 10:1 and participants who had been diagnosed with cholelithiasis prior to the index date matched 1:1. Cholelithiasis is a separate disease characterised by abdominal pain and not currently associated with glaucoma or IBS,²² serving as a negative comparison group. The matching was done with replacement. All participants diagnosed with glaucoma (by any definition) prior to their enrolment in the study were excluded from the analyses.

The DNRP Cohort data were analysed using a Cox proportional hazards regression analysis with robust variance estimators which accounts for repeated measures in the dataset. The index date was defined by the date that IBS was diagnosed in the index patient or the date for which IBS was diagnosed in the index patient in participants from the comparison groups. The IBS patients and the members of the two comparison cohorts were followed from index

date until the date of glaucoma, emigration, death or 30 November 2013, whichever came first. The hazard ratios (HRs) were controlled for age, sex and calendar period (by study design) and were adjusted for diagnoses of diabetes and sleep apnoea prior to the index date. For glaucoma described by medication data, models corrected for steroid usage are also presented to identify whether this is a significant indirect causation pathway in this study (Figure S1). Unadjusted and adjusted model results are presented for each outcome definition of glaucoma. As a sensitivity analysis, a lagged analysis for each outcome also was performed. In this analysis, patients with glaucoma diagnosed within 1 year of an IBS diagnosis were excluded.

A secondary analysis was performed with COPD taken as another potential confounder, as COPD is an illness strongly associated with smoking history.²³

The proportional hazard assumption was assessed and was not violated across the study period. The proportional hazards assumption was assessed graphically by log-log plots. All statistical analyses were performed using SAS version 9.2 (SAS Institute).

RESULTS

1958 UK Birth Cohort

Over 11,000 participants in the UKBC responded to one of the surveys administered at ages 42 and 50 years. Both the surveys completed at age 42 and 50 were completed by 9092 participants (52.2% of the original sample; Figure S2), one participant was excluded from the analysis due to incomplete data.

TABLE 1 Descriptive data for members of the 1958 UK Birth Cohort in total and by age at IBS diagnosis and glaucoma diagnosis

	IBS before/at age 42 (n = 778)	No IBS before/at age 42 (n = 8313)	Total (n = 9091)
Gender (female)	563 (72.4%)	4116 (49.5%)	4679 (51.5%)
IBS at age 50	162 (20.8%)	177 (2.1%)	339 (3.7%)
Glaucoma at age 50	9 (1.2%)	43 (0.5%)	52 (0.6%)
Incident glaucoma between ages 42 and 50	8 (1%)	40 (0.5%)	48 (0.5%)
Diabetes mellitus	45 (5.8%)	365 (4.39%)	410 (4.5%)
Ethnicity			
White	766 (98.5%)	8123 (97.9%)	8889 (97.8%)
Asian (including Indian)	4 (0.5%)	55 (0.7%)	59 (0.6%)
Black	3 (0.4%)	38 (0.5%)	41 (0.4%)
Other (including mixed decent)	5 (0.6%)	97 (1.2%)	102 (1.1%)
Smoking history at age 50 ^a			
Never smoked	339 (42.6%)	3920 (47.2%)	4259 (46.9%)
Ex-smoker	266 (34.2%)	2558 (30.8%)	2824 (31.1%)
Smoker	173 (22.2%)	1814 (21.8%)	1987 (21.9%)

Abbreviation: IBS, irritable bowel syndrome.

^aSmoking data were not available for 21 cases, none from the group who reported IBS at age 42.

TABLE 2 Results from the UK Birth Cohort examining the associations between IBS and glaucoma

Association	Bivariate OR (95% CI)	Multivariable-adjusted ^a OR (95% CI)	Multivariable-adjusted ^a model restricted to:	
			White population OR (95% CI)	Non-smokers OR (95% CI)
IBS before/at age 42, associated with incident glaucoma between ages 42 and 50	2.15 (95% CI:0.86–4.67)	1.96 (95% CI:0.78–4.33)	1.74 (95% CI:0.65–4.00)	2.07 (95% CI:0.69–5.16)
IBS at/before age 42 and at age 50, with incident glaucoma between ages 42 and 50	6.58 (95% CI:2.00–16.89)	5.82 (1.76–15.19)	5.95 (95% CI:1.78–15.60)	6.71 (95% CI:1.67–19.68)

Note: All data are presented as odds ratios with 95% confidence intervals.

Abbreviations: CI, confidence interval; IBS, irritable bowel syndrome; OR, odds ratio.

^aAdjusted for gender and comorbid diabetes mellitus.

Within this study population, 775 (8.5%) participants reported IBS at or before the age of 42. Chronic IBS was identified in 162 (1.8%) participants. Incident glaucoma, between the ages of 42 and 50 years, was identified in 48 (0.5%) participants. Characteristics of the study sample are presented in Table 1.

The ORs of developing glaucoma between the ages of 42 and 50 among the UKBC members with a diagnosis of IBS at or before the age of 42 compared to those without are presented in Table 2. In the unadjusted model, those with IBS at or before the age of 42 had more than twice the odds of receiving a diagnosis of glaucoma between ages 42 and 50 (OR: 2.15, 95% CI: 0.86–4.67), compared with those without IBS at or before the age of 42, although the result was imprecise. The association was marginally attenuated in the multivariable-adjusted model (OR: 1.96, 95% CI: 0.78–4.33). The IBS noted at or before the age of 42 was not associated with attrition by age 50.

The ORs of developing glaucoma between ages 42 and 50 in cohort members with a diagnosis of chronic IBS versus those without are presented in Table 2. In the unadjusted model, persons with chronic IBS had more than six times the odds of developing glaucoma (OR: 6.58, 95% CI: 2.00–16.89), compared with those without chronic IBS. This association was marginally attenuated in the fully adjusted multivariable-adjusted model (OR: 5.82, 95% CI: 1.76–15.19) and in multivariable-adjusted analyses restricted to the white population (OR: 5.97, 95% CI: 1.78–15.60).

When the analysis of the odds people with chronic IBS, for developing glaucoma between age 42 and 50, were limited to non-smokers, the elevated odds were not substantially altered (OR: 6.71, 95% CI: 1.67–19.68).

The Danish cohort analysis

The IBS was identified in 62,541 persons with records in the DNRP (0.85% of all persons in the Registry). The characteristics of the IBS and the comparison cohorts are presented in Tables 3 and 4.

During 499,761 person-years of follow up of IBS patients and 5,007,551 person-years of follow up of matched general population comparison cohort members, 176 IBS patients and 1334 general

population cohort members were found to have physician-diagnosed glaucoma. Glaucoma surgeries were identified for 69 IBS patients and 513 members of the comparison cohort. During 135,530 person-years of follow up of the IBS patients and 1,351,772 person-years of follow up of the matched comparison cohort in the 2005–2013 period (when medication data were available), 179 IBS patients and 1495 population cohort members were identified as initiating glaucoma medications.

Cumulative incidence curves with death as a competing risk are presented in Figure S3. After adjustment for potential confounders, a hospital diagnosis of glaucoma was more frequent in participants with IBS than in the population cohort (HR: 1.35, 95% CI: 1.16–1.56). The IBS patients were at similarly increased risk for glaucoma surgery (HR: 1.35, 95% CI: 1.06–1.70) and glaucoma medication use (HR: 1.19, 95% CI: 1.03–1.38). These results remained robust in the lagged analysis, which excluded patients whose glaucoma was diagnosed within 1 year of their IBS diagnosis (Table 5).

People with IBS more commonly used steroids in this cohort (Table 4). To identify the steroid-independent association, the model presented in Table 5 was further adjusted with minimal alteration to the association seen between IBS and glaucoma as defined by medication usage, with the HR of 1.18 (95% CI: 1.01–1.43). Lagged analysis was similarly unaffected (HR: 1.21, 95% CI: 1.04–1.42).

When the IBS cohort was compared with the comparison cohort diagnosed with cholelithiasis (Table 6), the association between IBS and physician-diagnosed glaucoma (HR: 1.24, 95% CI: 1.24–1.48) and the associations with glaucoma defined by surgical (HR: 1.69, 95% CI: 1.21–2.35) and medical interventions (HR: 1.29, 95% CI: 1.08–1.53) remained robust. When the medication definition was controlled for steroid use, the association was essentially unchanged (HR: 1.29, 95% CI: 1.09–1.53).

DISCUSSION

This study examined whether IBS was a risk factor for glaucoma in two large prospective European cohort studies. These data analyses reveal that a diagnosis of IBS was associated with an increased risk of

TABLE 3 Characteristics of the IBS patients identified from the DNRP and their matched comparison cohorts

	IBS cohort (n = 62,541)	Matched general population cohort (n = 625,410)	Cholelithiasis cohort (hospital comparison cohort) (n = 62,540)
Gender (female)	43,000 (68.8%)	430,000 (68.8%)	43,000 (68.8%)
Glaucoma			
Hospital diagnosis	176 (0.3%)	1334 (0.2%)	146 (0.2%)
Surgery	69 (0.1%)	513 (0.1%)	45 (0.1%)
Diabetes mellitus	2510 (4.0%)	19,294 (3.1%)	3797 (6.1%)
Sleep apnoea	415 (0.7%)	2003 (0.3%)	371 (0.6%)
Age at cohort enrolment			
<60	46,584 (74.5%)	465,720 (74.5%)	46,588 (74.5%)
60–69	8565 (13.7%)	85,925 (13.7%)	8563 (13.7%)
70–79	5163 (8.3%)	51,427 (8.2%)	5145 (8.2%)
80+	2229 (3.6%)	22,338 (3.6%)	2244 (3.6%)
Year of cohort enrolment			
1995–1999	13,058 (20.9%)	130,580 (20.9%)	13,058 (20.9%)
2000–2004	17,192 (27.5%)	171,920 (27.5%)	17,191 (27.5%)
2005–2009	17,770 (28.4%)	177,700 (28.4%)	17,770 (28.4%)
2010–2013	14,521 (23.2%)	145,210 (23.2%)	14,521 (23.2%)
Median years of follow-up (interquartile range)	7.6 (3.5–11.9)	7.6 (3.5–12.0)	7.6 (3.5–11.9)

Abbreviations: DNRP, Danish National Registry of Patients; IBS, irritable bowel syndrome.

TABLE 4 Characteristics of the IBS patients identified from the DNRP and their matched comparison cohorts during 2005–2013, when medication data were available

	IBS cohort (n = 32,291)	Matched general population cohort (n = 322,910)	Cholelithiasis cohort (hospital comparison cohort) (n = 32,291)
Gender (female)	22,247 (68.9%)	222,470 (68.9%)	22,247 (68.9%)
Glaucoma			
Medication initiation	179 (0.6%)	1495 (0.5%)	150 (0.5%)
Diabetes mellitus	1752 (5.4%)	13,092 (4.1%)	2527 (7.8%)
Sleep apnoea	348 (1.1%)	1681 (0.5%)	311 (1.0%)
Steroids usage (redeemed prescription)	5025 (15.5%)	30,931 (9.6%)	4174 (12.9%)
Age at cohort enrolment			
<60	24,417 (75.6%)	244,176 (75.6%)	24,419 (75.6%)
60–69	4505 (14.0%)	45,142 (14.0%)	4513 (14.0%)
70–79	2353 (7.3%)	23,344 (7.2%)	2335 (7.2%)
80+	1016 (3.1%)	10,248 (3.2%)	1024 (3.2%)
Median years of follow-up (interquartile range)	4.1 (1.9–6.5)	4.1 (1.9–6.5)	4.1 (1.9–6.5)

Abbreviations: DNRP, Danish National Registry of Patients; IBS, irritable bowel syndrome.

glaucoma in the UKBC and the DNRP. The UKBC found that people with IBS before or at the age of 42 and still at the age of 50 had an almost sixfold increase in the odds of developing glaucoma in this time

period, as compared to those who did not meet this definition of chronic glaucoma. The DNRP demonstrated that people who were diagnosed by a physician with IBS had a 35% increased risk of being

TABLE 5 Results for the IBS patients identified from the DNRP compared to a general population comparison cohort

Glaucoma definition	Cumulative incidence		Unadjusted hazard ratio ^a	Adjusted hazard ratio ^b
	General population cohort	IBS patients		
Physician diagnosis	0.47 (0.43–0.50)	0.72 (0.53–0.95)	1.36 (1.17–1.57)	1.35 (1.16–1.56)
Physician diagnosis (lagged)	0.45 (0.42–0.49)	0.70 (0.51–0.93)	1.32 (1.12–1.54)	1.30 (1.11–1.53)
Glaucoma surgery	0.24 (0.20–0.28)	0.28 (0.20–0.38)	1.37 (1.08–1.73)	1.34 (1.04–1.74)
Glaucoma surgery (lagged)	0.24 (0.20–0.28)	0.27 (0.19–0.37)	1.33 (1.04–1.70)	1.32 (1.03–1.68)
Glaucoma medication initiation	1.01 (0.94–1.09)	1.11 (0.94–1.30)	1.21 (1.04–1.40)	1.19 (1.03–1.38)
Glaucoma medication initiation (lagged)	0.94 (0.87–1.02)	1.04 (0.87–1.23)	1.23 (1.05–1.44)	1.21 (1.04–1.42)

Note: Data with 95% confidence intervals are presented for both the complete analysis and for the 1-year lagged sensitivity analysis.

Abbreviations: DNRP, Danish National Registry of Patients; IBS, irritable bowel syndrome.

^aControlled for matching factors (sex and birth year) by study design.

^bControlled for matching factors (sex and birth year) by study design and adjusted for diabetes mellitus and sleep apnoea diagnoses.

TABLE 6 Results from the DNRP: Risk of glaucoma in persons with IBS compared to those with cholelithiasis

Glaucoma definition	Cumulative incidence		Unadjusted hazard ratio ^a	Adjusted hazard ratio ^b
	Cholelithiasis cohort	IBS cohort		
Physician diagnosis	0.53 (0.43–0.66)	0.72 (0.53–0.95)	1.24 (1.04–1.47)	1.24 (1.04–1.48)
Glaucoma surgery	0.18 (0.12–0.26)	0.28 (0.20–0.38)	1.59 (1.16–2.18)	1.69 (1.21–2.35)
Glaucoma medication initiation	1.11 (0.86–1.40)	1.11 (0.94–1.30)	1.26 (1.07–1.49)	1.29 (1.09–1.53)

Note: Data are presented with 95% confidence intervals.

Abbreviations: DNRP, Danish National Registry of Patients; IBS, irritable bowel syndrome.

^aControlled for matching factors (sex and birth year) by study design.

^bControlled for matching factors (sex and birth year) by study design and adjusted for diabetes mellitus and sleep apnoea diagnoses.

diagnosed by a physician with glaucoma and similar increased risks of undergoing glaucoma surgery or having glaucoma medications initiated.

As the first investigation to explore this relationship, these findings should therefore be interpreted with caution and confirmed with replication studies. Similarly, given that glaucoma incidence was low in these studies, the clinical significance of these findings must be established with further research. Nevertheless, two Taiwanese studies have suggested a link between IBS and other neurodegenerative illness^{24,25} and so it is quite possible that IBS or some underlying mechanism inherent in its pathophysiology may have a negative impact on CNS homeostasis.

The authors suggest that the reason people with IBS are more likely to develop glaucoma could be due to two potential mechanisms: host-microbiome interactions or immune system dysregulation. Indeed, whether or not the current data are demonstrative of a causal link between IBS and glaucoma or rather a common causative pathway cannot be determined from this study and requires further research. Both of these proposed mechanisms are (as it pertains to IBS pathology) bidirectional and so disentangling the mechanism will require further experimental research.

Microbiome alterations associated with IBS² may be one potential cause of the elevated risk of glaucoma in the IBS patients. In support of this hypothesis, recent animal models have also suggested that changes in microbiome composition may impact on

glaucoma pathophysiology by modifying T cell-mediated immune effects.¹⁴ There are also multiple reports of reductions in the neurotrophin brain-derived neurotrophic factor, an important neuroprotective peptide for the optic nerve,^{26,27} in various other CNS regions in germ-free^{5,28} and dysbiosis mouse models⁶ (see Lee et al.²⁹ for review).

The second potential mechanism that may explain the association between IBS and glaucoma involves alterations in the immune system. Although IBS has traditionally been considered a brain-gut disorder with normal gut pathology, there is increasing evidence of altered immune homeostasis.^{30,31} This may play a role in glaucoma pathology. There is some indication that the IBS patients may have elevated inflammatory markers.³⁰ Moreover, in the IBS patients, increased amounts of circulating T cells activated by $\alpha 4\beta 7$ integrin molecules have been identified, implicating a certain degree of small intestinal inflammation in IBS.^{3,4}

The current research has several strengths. We were able to replicate our findings in two independent cohorts in different countries. Consistent with a dose-response relation, the association between 'chronic IBS' and glaucoma was stronger than the association between IBS at or before the age of 42, alone, and glaucoma. Similarly, in the DNRP-based study, IBS increased the hazard of glaucoma, and this was reiterated with multiple outcome definitions. The DNRP analysis also made use of a hospital comparison cohort, cholelithiasis, another disorder presenting with abdominal pain, to

address concerns regarding biases that may occur in reporting illnesses to national registries. The analysis produced consistent results.

There are some weaknesses to note in this investigation. The UKBC provided limited time points to capture IBS and glaucoma data, and the data contained in this study are based on self-reported questionnaire responses. Similarly, while the DNRP provided dates of each hospital diagnosis, allowing for a clearer understanding of the timeline, the left-truncation problem that occurs with hospital-based registries may have occurred here also and therefore future studies are warranted to understand the timeline of this association. Although the majority of the glaucoma patients have primary open-angle glaucoma,⁸ the authors were unable to determine the subtypes of glaucoma affecting the IBS patients that we identified in the UKBC. In the DNRP, although the physician-diagnosed definition of glaucoma was limited to primary open-angle glaucoma, the surgical and medication definitions are unable to be limited by subtype. Future research is needed to examine whether this relationship is more strictly related to certain IBS subtypes or certain glaucoma phenotypes. If the microbiome is responsible for the effects seen, future investigation of this association should attempt to dissect which IBS subtypes primarily contribute to this finding, as the microbiome may differ between IBS subtypes.²

Known risk factors for glaucoma and IBS have relatively limited overlap, minimising the potential for confounding. While gender and age were clear confounders of the association, the other covariates did not appear to confound the association, with effect sizes remaining essentially unchanged even in multivariable-adjusted analyses. The effect of racial background on this association was difficult to evaluate in these relatively racially homogeneous cohorts. The results may be reliably applied to white populations, but generalisation to other populations should be done with caution. Unmeasured confounding analysis (see Supporting Information S1) demonstrated that unmeasured confounders would need large effect sizes to account for these results.

Future research is warranted to assess the association between IBS and glaucoma. If IBS is simply a marker of an underlying causative mechanism that also plays a role in development of glaucoma, there may be no explicit causative chain between IBS and glaucoma. Nevertheless, this study remains useful for its potential screening implications and also for informing the development of further research projects that investigate this link mechanistically. A greater understanding of this association may lead to interesting glaucoma treatment options, especially for people with IBS. It is also important to investigate whether IBS patients are at elevated risk for developing other neurodegenerative illnesses.^{24,25}

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CONFLICT OF INTEREST

No authors have any conflicts of interest to report.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are openly available as described in the [Methods](#) section of this article.

ORCID

Zachary E. McPherson  <https://orcid.org/0000-0001-9072-013X>

Mark A. McEvoy  <https://orcid.org/0000-0002-5505-5557>

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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